REMARKS

Claims 1-6 and 8-24 appear in this application for the Examiner's review and consideration. A Declaration of Raphael Bar ("the Bar Declaration") is submitted with this response.

Claims 1-10, 15, 16, and 18-24 were rejected under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 5,284,867 to Kloog et al. ("Kloog") for the reason set forth on page 2 of the Office Action. The Examiner maintains that Kloog discloses the compound of the present invention, essentially free of the (3R, 4R) enantiomer, various pharmaceutical formulations for various types of administrations, and methods of use for treating neurological disorders (page 2). The Examiner also states that the formulation is emulphor or emulsions and may contain antioxidants, and that Kloog also discloses various percentage combinations of the emulsions.

Applicants stress that Kloog does not disclose or teach HU-211 having the (3S,4S) configuration and being in enantiomeric excess of at least 99.90% over the (3R,4R) enantiomer, as presently claimed. Kloog's HU-211 and the HU-211 claimed are significantly different compounds with different properties, which are attributable to the differences in enantiomeric purity. Kloog reports that the inventors discovered that HU-211 at about 25 mg/kg per body weight, administered most likely to mice, induced stereotypy, locomotor hyperactivity and tachycardia (Col. 5, lines 26-32). In contrast, the compound of the present invention was administered at single doses of 50 mg/kg in rats, 25 mg/kg in rabbits and 50 mg/kg in monkeys, with no observed adverse effects (Specification at page 33, lines 26-28). The present compounds can be administered advantageously at higher doses, without causing deleterious side effects.

Kloog discloses the compound HU-211 (dexanabinol), *i.e.* the (3S,4S) enantiomer of 1,1-dimethylheptyl-(3S,4S)-7-hydroxy-Δ^6-tetrahydrocannabinol, which is 'essentially free' of the (3R,4R) enantiomer. The Examiner argues that the compound of Kloog has an enantiomeric excess of 99.90% over the (3R,4R) enantiomer, since there is no evidence or showing to the contrary. Applicants respectfully disagree. Enantiomeric excess is different from purity in general and is derived from the following formula:

percent enantiomeric excess = 100 x ([HU-211] - [HU-210])/([HU-211] + [HU-210])

wherein the concentration of the enantiomers is separately determined by HPLC and expressed as percent by weight.

In the previous response, Applicants submitted a Declaration of Avihai Yacovan. The Yacovan Declaration included evidence supporting Applicants' position that the compound of Kloog is substantially different in its properties from the claimed compound. In particular, it was shown that the compound of Kloog caused a drastic drop in rectal temperature, almost totally inhibited spontaneous locomotion, and caused significant catalepsy, while the claimed compound did not exhibit any of these adverse effects.

The Examiner contends that these results are not persuasive because the study was not a true side-by-side comparison. The Examiner insists that the Mechoulam sample described in the Yacovan Declaration does not represent a true Kloog sample.

U.S. Patent No. 4,876,276 to Mechoulam et al. discloses the laboratory scale synthesis of HU-211. Applicants note that Kloog does not teach the synthesis of HU-211, but only describes that the acetylation of HU-211 results in a mixture of HU-211, HU-247, compound A, and compound B (Col. 6, lines 10-65). Kloog also teaches that HU-211 can be recovered as the starting material by reducing compounds A and B with $LiAlH_4$ (Col. 6, lines 66-67). As there is no synthetic route disclosed in Kloog, it is understood that Kloog's HU-211 was prepared by Professor Raphael Mechoulam, a co-inventor in Kloog (Bar Declaration, ¶ 6). Thus, the compound disclosed in Kloog is a sample that was prepared according to procedures known and used by Mechoulam. In this case, Applicants understand that the compound of Kloog was prepared according to the original synthetic procedure developed by Mechoulam (*Id.*).

The Mechoulam sample described in the Yacovan Declaration was prepared according to a slightly modified version of Mechoulam's original synthetic procedure (*Id.*). Indeed, the Mechoulam sample obtained by the modified procedure either corresponds to the Kloog sample or is even superior to the Kloog sample, such that comparison of a true Kloog sample with the Ultrapure sample that is covered by the claims of this application would have been even more favorable to the Ultrapure sample (*Id.*). Applicants therefore submit that the Mechoulam sample is comparable to and does represent the Kloog sample.

The Mechoulam sample was tested and found to contain 91.1% HU-211 and 0.26% HU-210, yielding an enantiomeric excess of 99.4% (*Id.* at ¶ 7), which is less than the at least 99.90% claimed. Consequently, Kloog cannot anticipate the claimed invention because it does not teach or disclose each and every feature in the claims. Accordingly, this rejection under 35 U.S.C. § 102(b) has been overcome and should be withdrawn.

Claims 1-6 and 8-24 were rejected under 35 U.S.C. § 103(a) as obvious over Kloog for the reasons set forth on pages 3 and 4 of the Office Action. Specifically, the Examiner notes that the difference between the claimed invention and Kloog is that the claims recite a compound having (3S, 4S) enantiomeric excess of at least 99.90% over the (3R, 4R) enantiomer, while Kloog teaches that the compound is essentially free of the (3R, 4R) enantiomer. The Examiner further argues that the difference between 99.4 % enantiomeric excess in the Kloog sample and 99.9% enantiomeric excess in the claimed compound is within experimental error and/or design.

Applicants respectfully disagree. As laid out and explained above, the Yacovan Declaration clearly provides the requisite evidence the Examiner is seeking. Applicants stress again that the percentages referred to by the Examiner are not absolute purities, but are enantiomeric excess percentages derived from the formula provided above. Kloog does not disclose any importance to achieving a 99.9% enantiomeric excess and does not disclose a process for obtaining such excess.

Applicants assert that the difference between 99.4% and 99.9% is not within experimental error. As described previously, this distinction results in significantly different biological properties of HU-211 (*Id.* at ¶ 8). Animals that were administered the Mechoulam sample displayed dramatic hypothermia, catalepsy, and locomotor inhibition (*Id.*). In contrast, animals that were treated with the Ultrapure sample did not exhibit any of these adverse side effects (*Id.*).

The presence of only 0.26% HU-210 (a seemingly small amount) is enough to cause these serious side effects (*Id.*). This demonstrates the need to develop a different route of synthesis to achieve the level of purity appropriate for safe administration of HU-211 (*Id.*). The Mechoulam sample that was prepared according to Mechoulam's synthetic route simply does not provide above 98% absolute amount of HU-211 and below 0.05% absolute amount of HU-210, to yield an enantiomeric excess of above 99.90% (*Id.*).

Furthermore, in order to obtain this excess, Applicants discovered a new route of synthesis to prepare compounds with that property. As described in the Specification, the crystallization performed in the last step of the synthesis of dexanabinol is crucial for the purity of the final product. Specifically, the product of the last step is recrystallized from acetonitrile and then from a 1:1.2 water : ethanol mixture (*See* Specification at page 20, lines 5-8).

In addition, while 99.4% and 99.9% appear at first glance to be very close in value, these values refer to calculated enantiomeric excess percentages that do not reflect the original absolute amounts of the individual enantiomers (Bar Declaration, ¶ 9). The content of HU-211 in the Mechoulam sample is 91.1%, while that in the Ultrapure sample is 98.8%. This is a difference of more than 7.5% (*Id.*). The content of HU-210 in the Mechoulam sample at 0.26% is more than 10 times that in the Ultrapure sample (*Id.*). These differences in content are not attributable to experimental variation, and are certainly more than a person of skill in the art would accept from validated analytical methods (*Id.*).

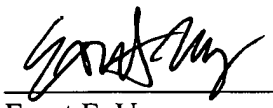
Applicants also developed analytical methods accurate and sensitive enough to detect the differences in absolute amounts of HU-210 and HU-211 (*See* Specification at page 8, lines 22-29 and Bar Declaration, ¶ 10). Past methods could not determine the amount of these enantiomers accurately, especially the small amount of HU-210 (Bar Declaration, ¶ 10). Applicants' methods allow detection of HU-210 at a concentration of as low as 0.125 μL (*Id.*). The two linearity plots presented in the Bar Declaration illustrate both the accuracy and sensitivity of these methods. The superiority of these methods demonstrate that the absolute amounts of HU-210 and HU-211 in the Mechoulam and Ultrapure samples are not within experimental error, and consequently, neither are the enantiomeric excess percentages (*Id.*).

For all these reasons, this rejection under 35 U.S.C. § 103(a) has been overcome and should be withdrawn.

Accordingly, Applicants believe that the application is now in condition for allowance, early notice of which would be appreciated. Should any issues remain, the Examiner is invited to contact the undersigned attorney of record in an effort to expedite the processing of this application.

Respectfully submitted,

Date: 3/6/06



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